REMARKS

Status Summary

Claims 1, 2, 4-15, 20-22, 26-28, 30, 31, 34-40, 46-48, 52, 55-65, 70-72, and 75 are pending in the present application. Claims 1, 2, 4-15, 20-22, 26-28, 30, 31, 34-40, 46-48, 52, 55-65, 70-72, and 75 presently stand rejected.

Claims 1, 2, 5, 9, 11, 12, 20, 21, 27, 28, 31, 35, 37, 38, 46, 47, 55, 56, 58, 60, 62, 63, 70, and 71 have been amended. New Claims 78 and 79 have been added. No new matter was added by the amendments or the addition of new claims.

Claim Rejection – 35 U.S.C. § 112, First Paragraph

Claims 1, 2, 4-15, 20-22, 26-28, 30, 31, 34-40, 46-48, 52, 55-65, 70-72, and 75 have been rejected by the United States Patent and Trademark Office (hereinafter "the Patent Office") under 35 U.S.C. § 112, first paragraph, upon the contention that the rejected claims fail to meet the "written description" provision of 35 U.S.C. § 112, first paragraph. More particularly, the Patent Office contends that because of the phrases "a biologically active derivative" of an antimicrobial peptide and "a part thereof, an analogue thereof, and a homologue thereof", the rejected claims are broader than what is discussed in the specification. See the Official Action at page 3. The Patent Office also contends that to the extent the claimed subject matter is not adequately described in the instant disclosure, the same claims are also rejected under the "enablement requirement" of 35 U.S.C. § 112, first paragraph.

With regard to the phrase "a part thereof, an analogue thereof, and a homologue thereof", applicants respectfully submit the phrase is supported by the specification and meets the written description and enablement requirements of 35 U.S.C. § 112, first paragraph. However, in an effort to expedite prosecution, applicants have amended all occurrences of the phrase in the pending claims to delete the phrase "a part thereof, an analogue thereof, and a homologue thereof".

Claim 1 and subsequent independent claims now recite "a preform thereof, a preproform thereof, a biologically active peptide derived therefrom". Support for the

amendment can be found throughout the specification and in particular at page 9, lines 9-12, wherein it is disclosed the therapeutic antimicrobial peptides include biologically active peptides derived therefrom. The specification also recites specific examples of biologically active peptides derived from the listed therapeutic antimicrobial peptides. In particular, the specification teaches beginning at page 9, line 24 that melittin derivatives having at least the C-terminal six amino acids removed maintain biological activity similar to that of melittin. Also, beginning at page 4 line 7 the specification teaches that Shiva-1, an analogue of cecropin, shares 40% sequence homology with cecropin and maintains biological activity similar to cecropin, i.e. the ability to lyse cells. Further, the claims as originally filed and the specification provide specific examples of preforms and preproforms of the antimicrobial peptides, including premelittin, prepromelittin, prececropin, and preprocecropin. See specification at page 9, lines 9-12 and elsewhere.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed in invention. See *Vas-Cath, Inc. v. Mahurkar*, 19 U.S.P.Q.2d 1111,1116 (Fed. Cir. 1991). There is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed. *In re Wertheim*, 191 U.S.P.Q. 90, 96 (CCPA 1976). With regard to the phrase "a biologically active derivative", applicants respectfully submit the phrase is supported by the specification and meets the written restriction and enablement requirements of 35 U.S.C. § 112, first paragraph. Indeed, applicants further respectfully submit, that presently recited claim language "a preform thereof, a preproform thereof, a biologically active peptide derived therefrom" is specifically taught by the specification, including through the recitation of multiple examples of specific biologically active peptides derived from the claimed therapeutic antimicrobial peptides, preforms thereof and preproforms thereof. As such, the presently disclosed subject matter is described with sufficient detail by the specification that one skilled in the art would reasonably conclude the inventors had

possession of the claimed peptides, and therefore the presently disclosed subject matter meets the written description requirement.

Applicants further submit the presently disclosed subject matter meets the enablement requirements of 35 U.S.C. § 112, first paragraph as well. 35 U.S.C. § 112, first paragraph, requires no more than a disclosure sufficient to enable one skilled in the art to carry out the invention commensurate with the scope of the claims. Applicants respectfully submit this requirement has clearly been met. As discussed above, the specification teaches several examples of biologically active peptides derived from the claimed therapeutic antimicrobial peptides, as well as preforms and preproforms of the claimed therapeutic antimicrobial peptides. Further, it is clear, particularly in light of the art of record discussed by the Patent Office in the Official Action (at page 3), that it would have been within the general knowledge of one of skill in the art at the time of filing of the present application to determine without undue experimentation whether a particular peptide derived from the claimed therapeutic antimicrobial peptides had biological activity. For example, the Patent Office cites at page 3 of the Official Action passages from the journal articles by *Rivett et al.* (Biochem J. 1996; 316: 525-29) and *Perez-Paya et al.* (J. Biochem 1995), and U.S Patent 6,255,282 to *Jaynes et al.* which each disclose measurement of changes in biological activity, including loss of activity, of peptides derived from the therapeutic antimicrobial peptides recited in the present claims. Therefore, it is clear from these citations that it was within the capacity of one skilled in the art at the time of filing the present application to determine without undue experimentation whether a particular peptide derived from the claimed therapeutic antimicrobial peptides possessed biological activity. As such, applicants respectfully submit the presently disclosed subject matter meets the enablement requirement of 35 U.S.C. § 112, first paragraph.

In summary, without acquiescing to the establishment of proper *prima facie* rejections of the presently pending claims under the written description and enablement requirements of 35 U.S.C. § 112, first paragraph, applicants have amended the claims to recite the phrase "a preform thereof, a preproform thereof, a

biologically active peptide derived therefrom". Applicants have set forth rationale as to why the presently disclosed subject matter also meets the written description and enablement requirements of 35 U.S.C. § 112, first paragraph. As such, applicants respectfully request the Patent Office withdraw the rejection of Claims 1, 2, 4-15, 20-22, 26-28, 30, 31, 34-40, 46-48, 52, 55-65, 70-72, and 75 under 35 U.S.C. § 112, first paragraph, and allow the claims at this time.

Claim Rejection – 35 U.S.C. § 112, Second Paragraph

Claims 1, 2, 4-15, 20-22, 26-28, 30, 31, 34-40, 46-48, 52, 55-65, 70-72, and 75 have been rejected by the Patent Office under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. More particularly, the Patent Office contends that the phrases "a biologically active derivative" of an antimicrobial peptide and "a part thereof, an analogue thereof, and a homologue thereof" are vague and indefinite because "the lower limits of the part and the homologue have not been specified, the extent of variation of an analogue is not specified [and] . . . [f]urther, the specification fails to teach how to determine whether a peptide is derived from melittin or cecropin, it is unclear what is encompassed or excluded by these terms, thus the metes and bounds of the claims could not be readily determined." Official Action at page 6.

As previously discussed, and without acquiescing to the legitimacy of the rejections, applicants have canceled the phrases "a biologically active derivative" of an antimicrobial peptide and "a part thereof, an analogue thereof, and a homologue thereof" in order to expedite prosecution of the pending application. Therefore, the rejection has been rendered moot. As such, applicants respectfully request withdrawal of the rejection of claims 1, 2, 4-15, 20-22, 26-28, 30, 31, 34-40, 46-48, 52, 55-65, 70-72, and 75 have been rejected by the Patent Office under 35 U.S.C. § 112, second paragraph, as being indefinite.

Applicants have also amended the pending claims to include the phrase "a preform thereof, a preproform thereof, a biologically active peptide derived

therefrom". Applicants submit this phrase is not vague or indefinite since as previously discussed, it was within the knowledge of one skilled in the art to determine whether a particular peptide derivative possessed biological activity. Such biological activities were well known and easily measurable at the time of filing of the present application. Further, it is clear the biological activity would be commensurate with the scope of the therapeutic peptide from which it was derived, i.e. antimicrobial activity. As such, the phrase "a biologically active peptide thereof" as recited in the pending claims is clear and definite.

The Patent Office has also rejected Claims 12, 38, and 63 because, as the Patent Office contends, the phrase "the U3 sequence" has insufficient antecedent basis. Applicants note the insufficient antecedent basis resulted from an error in the dependency of the claims from which the rejected claims depend. The claim dependencies have been corrected by the present amendment. Specifically, Claims 11, 37, and 62 have been amended to recite proper dependency from Claims 10, 36, and 61, respectively. Further, Claims 12, 38, and 63 have been amended to change the phrase "the U3 sequence" to "the U3 region" so as to recite the element more precisely as set forth in the claims from which Claims 12, 38, and 63 ultimately depend. The correction in dependency and phrasing are believed to correct the improper antecedent basis. As such, applicants respectfully request the Patent Office withdraw the rejection of Claims 12, 38, and 63.

The Patent Office has also rejected Claims 13, 39, and 64 because, as the Patent Office contends, the phrase "said polylinker" has insufficient antecedent basis. Applicants note the insufficient antecedent basis resulted from an error in the dependency of the claims from which the rejected claims depend. The claim dependencies have been corrected by the present amendment, as discussed above. Specifically, Claims 11, 37, and 62 have been amended to recite proper dependency from Claims 10, 36, and 61, respectively. The correction in dependency is believed to correct the improper antecedent basis. As such, applicants respectfully request the Patent Office withdraw the rejection of Claims 13, 39, and 64.

The Patent Office has also rejected Claims 21 and 71 as being "vague and indefinite because of the claim recitation, 'a RNA produced by a vector', wherein the vector is a retroviral vector DNA." Official Action at page 7. The Patent Office argues "it is unclear how a DNA vector produces a RNA, thus, the metes and bounds of the claims are uncertain." *Id.* The basis for this rejection is not clear. It was known to one skilled in the art at the time of filing the present application that DNA, such as DNA in a vector, can be transcribed by a polymerase to produce an RNA molecule. As such, applicants believe the phrase that forms the basis of this rejection is not indefinite. However, if the Patent Office has a suggestion for an appropriate amendment of the phrase, applicants would gratefully consider the suggestion. In the meantime, applicants respectfully request withdrawal of the rejection of Claims 21 and 71.

Claim Rejection - 35 U.S.C. § 102(e)

Claims 1, 9, 11, 14, 15, 20-22, 26, 27, 35, 37, 40, 46-48, and 52 stand rejected by the Examiner under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,022,735 to Curiel et al., hereinafter referred to as "Curiel et al.".

The Patent Office argues Curiel et al. teaches, *inter alia*, a retroviral DNA vector (pCMVL) encoding and expressing melittin. See Official Action at page 7.

The positions of the Patent Office as summarized above with respect to Claims 1, 9, 11, 14, 15, 20-22, 26, 27, 35, 37, 40, 46-48, and 52 are respectfully traversed as described below.

"A claim is anticipated only if each and every element in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The rejected claims all pertain, *inter alia*, to a recombinant retroviral vector comprising one or more coding sequences which encode a therapeutic antimicrobial peptide. The encoded peptide can be melittin.

Applicants respectfully submit Curiel et al. does not teach each and every element of any of the rejected claims. First, the Patent Office asserts the vector

pCMVL is a retroviral vector. Applicants respectfully disagree with this assertion. Curiel et al. teaches pCMVL is a "reporter gene construct containing the Photinus pyralis luciferase gene under the control of the cytomegalovirus promoter". Curiel et al. at col. 35, lines 40-42. The luciferase gene was transferred into the plasmid pSTCX556 as a Klenow-treated fragment from the plasmid pRSVL to produce pCMVL. See Curiel et al. at col. 35, lines 25-51. It appears then from the teachings of Curiel et al. that although pRSVL could be characterized as a retroviral vector, as it contains the Rous Sarcoma Virus LTR Enhancer/Promoter (col. 35, lines 25-30), only the luciferase gene was utilized from pRSVL to create pCMVL, and therefore pCMVL is not a retroviral vector.

Assuming *arguendo* pCMVL is a retroviral vector, applicants respectfully assert Curiel et al. still does not teach each and every element of any of the rejected claims. Specifically, Curiel et al. does not teach that pCMVL (or any other vector) encodes and expresses melittin, as asserted by the Patent Office.

Curiel et al. teaches a composition for increasing efficiency of transfection of eukaryotic cells, comprising complexes of nucleic acids, a substance having an affinity for nucleic acid, and an internalizing factor such as a virus, containing or acting alone as an "endosomolytic agent". The endosomolytic agent helps release the contents of the endosome into the cytoplasm, which increases the nucleic acid transfer capacity. See Curiel et al. Abstract. In some of the Examples, pCMVL was used as the nucleic acid in transfection experiments. As discussed above, Curiel et al. teaches that pCMVL encodes luciferase under the control of a cytomegalovirus promoter. pCMVL was transfected into cells and luciferase activity occurred as a result of luciferase gene expression encoded by pCMVL and was measured as an indicator of transfection efficiency. See Curiel et al., Example 6 generally, and col. 41, lines 9-14 and 28-40 in particular; see also Curiel et al., Example 7 generally, and col. 42, lines 45-65 in particular.

In Example 35, Curiel et al. teaches using non-viral agents as endosomolytic agents (see Example 35 heading). The non-viral endosomolytic agents utilized in Example 35 include melittin, and each was synthesized prior to the experiment on an

automatic synthesizer. See Curiel et al. at col. 71, lines 4-58. The DNA to be transfected (pCMVL) was then combined with the non-viral endosomolytic peptide (e.g. melittin) prior to transfection of the complex. See Curiel et al. at col. 73, lines 31-47 and col 73, line 63-col 74, line 5. Table 3 shows the titration determination of the optimal amount of endosomolytic agent to be used for transfection, with 6 µg pCMVL added for each titration, 0-30 µg poly-lysine added (as shown in the top row), and 0-20 µg endosomolytic agent, e.g. melittin, added (as shown in the left column).

Therefore, Curiel et al. does not teach that pCMVL encodes and expresses melittin, as asserted by the Patent Office. Rather, melittin was synthesized prior to the experiment on an automatic synthesizer and then added to a quantity of the pCMVL plasmid to form part of a complex utilized in transfection experiments.

In summary, applicants respectfully submit the pCMVL vector taught by Curiel et al. is not a retroviral vector. Further, even assuming *arguendo* pCMVL is a retroviral vector, pCMVL does not encode a therapeutic antimicrobial peptide, e.g. melittin, as recited in the rejected claims. Therefore, since Curiel et al. does not teach each and every element of Claims 1, 9, 11, 14, 15, 20-22, 26, 27, 35, 37, 40, 46-48, and 52, applicants respectfully submit that maintaining a rejection under 35 U.S.C. § 102(e) based on Curiel et al. is improper. Withdrawal of the rejection of Claims 1, 9, 11, 14, 15, 20-22, 26, 27, 35, 37, 40, 46-48, and 52 under 35 U.S.C. § 102(e) as being anticipated by Curiel et al., is therefore respectfully requested. Allowance of Claims 1, 9, 11, 14, 15, 20-22, 26, 27, 35, 37, 40, 46-48, and 52 is also respectfully requested.

Claim Rejection - 35 U.S.C. § 103(a)

Claims 1, 2, 4-15, 20-22, 26-28, 30, 31, 34-40, 46-48, 52, 55-65, 70-72, and 75 stand rejected by the Patent Office under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,962,410 to Jaynes et al. (hereinafter referred to as "Jaynes et al.") in view of U.S. Paent No. 5,658,775 to Gilboa et al. (hereinafter referred to as "Gilboa et al.") and U.S. Patent No. 6,027,722 to Hodgson et al. (hereinafter referred to as "Hodgson et al.").

The Patent Office argues that Jaynes et al. teaches peptides including cecropin and melittin useful for inhibition of eukaryotic pathogens and neoplastic cells. The Patent Office further argues Jaynes et al. teaches that the peptides could be delivered via a retroviral vector encoding the peptide to the cells of interest. However, the Patent Office admits Jaynes et al. does not teach the details of how such a retroviral expression vector could be constructed. See Official Action at page 8. The Patent Office then argues that Gilboa et al. teaches constructing a retroviral vector, wherein the vector comprises *inter alia* at least a portion of a retrovirus including both the 5' retroviral LTR region and the 3' LTR region containing the U3-R-U5 structure. However, the Patent Office admits Gilboa et al. does not teach either expressing the peptides recited by the pending claims, including cecropin and melittin, or complete deletion of the U3 region, as recited in some of the pending claims. See the Official Action at pages 8-9. The Patent Office then argues that Hodgson et al. teaches a 5' LTR "comprising the U3-R-U5 structure and a 3' LTR comprising the U3-R-U5 structure, wherein the U3 is partially or completely deleted and replaced with a sequence which comprises at least one unique restriction site (fig 2a) and at least one insertion of a heterologous DNA fragment opaerably linked to a promoter (figs. 4, 5)." Official Action at page 9. However, Hodgson et al. does not teach or suggest a retroviral vector DNA comprising one or more coding sequences which encode a therapeutic antimicrobial peptide, as recited in the present claims.

It thus appears that none of the cited references alone teaches or suggests each and every element of any of the presently pending claims. However, the Patent Office argues that it would have been obvious to one skilled in the art at the time the invention was made "to employ the retroviral vectors taught by Gilboa et al, and Hodgson et al et al [sic], in the method of Jaynes et al for expressing a lytic peptide in animal cells with a reasonable expectation of success." Official Action at page 9.

The positions of the Patent Office as summarized above with respect to Claims 1, 2, 4-15, 20-22, 26-28, 30, 31, 34-40, 46-48, 52, 55-65, 70-72, and 75 are respectfully traversed as described below.

The Patent Office provides as the sole motivation for combining the references of Jaynes et al. with Gilboa et al. and Hodgson et al. that "because given the numerous retroviral vectors known in the art, it is within the levels of the reasonably skilled to use an appropriate vector for expressing a gene of interest." Official Action at pages 9-10 (emphasis added). However, applicants respectfully note that the level of skill in the art cannot be relied upon to provide the suggestion to combine references. See MPEP 2143.01 and *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999). As the Court of Appeals for the Federal Circuit held in In re Rouffet, a base statement such as "the level of ordinary skill in the art was high" is insufficient to provide the requisite motivation to combine references. See In re Rouffet, 47 U.S.P.Q.2d 1453 (Fed. Cir. 1998). The court stated:

> If such a rote invocation could suffice to supply a motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a patentable technical advance. Instead, in complex scientific fields, the Board could routinely identify the prior art elements in an application, invoke the lofty level of skill, and rest its case for rejection. To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness.

Id. at 1458.

Applicants respectfully submit the Patent Office has not provided a valid motivation for combining the references of Jaynes et al., Gilboa et al., and Hodgson et al. Applicants therefore respectfully submit the Patent Office has not established a *prima facie* case of obviousness for rejecting the pending claims over Jaynes et al. in combination with Gilboa et al. and Hodgson et al. As such, applicants respectfully request withdrawal of the rejection of Claims 1, 2, 4-15, 20-22, 26-28, 30, 31, 34-40, 46-48, 52, 55-65, 70-72, and 75 as obvious over Jaynes et al. in combination with Gilboa et al. and Hodgson et al. Allowance of Claims 1, 2, 4-15, 20-22, 26-28, 30, 31, 34-40, 46-48, 52, 55-65, 70-72, and 75 is also respectfully requested.

New Claims

New claims 78 and 79 have been added by this amendment as indicated above.

Claims 78 and 79 are independent claims derived from Claims 2 and 5, respectively, essentially rewritten to additionally provide that a biologically active peptide derived from the recited therapeutic antimicrobial peptides has antimicrobial activity. Support for the new claims can be found in Claims 2 and 5 and throughout the specification.

It is respectfully submitted that new claims 78 and 79 are allowable over the prior art. No new matter is considered to have been added.

CONCLUSION

In light of the above amendments and remarks, it is respectfully submitted that the present application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above Remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

Serial No.: 08/999,690

DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any fees associated with the filing of this correspondence to Deposit Account No. **50-0426**.

Respectfully submitted,

JENKINS, WILSON & TAYLOR, P.A.

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